REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

Claim 1 is currently being amended.

Claims 2-7, 18-26, and 29-30 are withdrawn.

Claims 8-15 were cancelled.

New Claims 31-40 are being added. Withdrawn claims 8-15 are redrafted in new claims 31-38.

After amending the claims as set forth above, claims 1, 16, 17, 27, 28 and 31-40 are pending in this application.

Rejection under 35 USC § 112, first and second paragraphs

Claims 1-30 are rejected for alleged lack of enablement. Applicants respectfully traverse this rejection. Section 112 mandates that patent applications describe the "manner and process of making and using" the invention. The courts have considered applications to be in compliance with section 112 where the person of skill in the art can practice the invention without **undue** experimentation. *See In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The test for compliance with §112 is not whether experimentation is necessary, but whether any experimentation would be undue in view of what type and amount of experimentation are usual in the field. *See In re Wands*, 858 F.2d at 736-37 ("Enablement is not precluded by the necessity for some experimentation such as routine screening."). *See also* MPEP § 2164.01 (Rev. 2, July 1996) at page 2100-135, column 2. Routine design choices cannot be equated with non-enablement. The courts have recognized that absolute predictability is not a requirement for §112. The burden to establish an enablement rejection rests with the examiner. *See In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (*citing In re Marzocchi*, 169 USPQ 367, 369-70 (CCPA 1971)); MPEP § 2164.04 (Rev. 2, July 1996). The examiner has not met this burden.

The Examiner alleges that the specification only teaches "examples of identifying framework proteins suitable for further modification." However, the specification does provide

support for proteins engineered using the claimed method. Figures 1, 2, 9, 11 and 14 along with examples from the specification such as the example found on page 27 lines 12-19, , are replete with examples of engineered framework proteins. Using the guidance in the specification, one of skill in the art could create additional engineered proteins, without undue experimentation. Accordingly, applicants believe that this rejection is improper.

Claim 1 was rejected under § 112, second paragraph. The examiner alleged that claim 1 recited a method of protein engineering but lacked steps that would lead to an engineered protein; claim 1 has been amended to recite "A method for identifying a framework protein for subsequent engineering." Accordingly, applicants believe that the withdrawal of claim 2 combined with amended claim 1 overcomes this rejection because the present claim 1 recites steps to identify framework proteins for subsequent engineering.

Additionally, applicants have redrafted claim 8 as independent claim 31 adding step (iv) which recites the modification of the framework protein identified by the database searching procedure. Because step (iv) discloses an engineering step and thus, would provide an engineered protein, claim 31 covers a method of protein engineering. As explained above, support for claim 31 is found in figures 1, 2, 9, 11 and 14 along with the accompanying examples.

Claims 11-13 were rejected under § 112, second paragraph for reciting a protein with greater stability but allegedly lacking the comparison step necessary to establish the proteins greater stability. Claims 34-36 (former claims 11-13) have been redrafted to include a comparison step. The redrafted claims separately cover determining whether the engineered framework protein has greater stability, increased structural similarity, or inhibitory function compared to the sample protein. Claims 29-30 have been withdrawn without prejudice. Accordingly, applicants believe that the presently amended claims overcome this rejection.

Rejection under 35 USC § 102(a)

The examiner has rejected claims 1-14, 16-19, 27 and 28 as anticipated by Wilson et al, WO 97/41526. Applicants respectfully disagree with the examiner. Wilson uses the precise three dimensional coordinates of a subset of atoms in a specific peptide (based on crystal structure) and database searching programs such as MACCS-3D and Sybyl 3-D. In contrast, the presently

claimed invention identifies, as a as a Cα-Cβ vector, the three-dimensional location and orientation of each amino acid side chain.

Further, the method of Wilson teaches searching for molecules using multiple queries, comprising atom subsets from the peptide GGTYSCHFGPLTWVCKPQGG. In contrast, the presently claimed invention can be performed using a single query. Unlike Wilson, which relies on a direct hit method and does not contemplate subsequent engineering, the present invention finds the largest subset of matches between a query and a database protein and uses this information to find a framework for subsequent protein engineering.

Additionally, applicants note that the D1 region described in Wilson relates to the N-terminal domain of the EPO-binding protein (the sample protein) and not to the framework protein entry in the database to be searched as recited in present claims 1 and 31. In fact, Wilson provides no teaching with regards to selecting the molecule types present in the database to be searched. Moreover, Wilson does not teach a database containing entries in the form of a description of a location and orientation in 3D space of side chains of the amino acid residues of a framework protein comprising 70 amino acids or less with 1-11 disulfide bonds, wherein the location and orientation of each side chain is simplified as a Cα-Cβ vector, as recited in the present invention.

With regard to claims 27 and 28, applicants argue that Wilson does not teach a computer program capable of searching a database comprising a plurality of entries, each said entry corresponding to a distance matrix representation of two or more Cα-Cβ vectors, using steps (i) and (ii) of claim 27 or the filtering step recited by claim 28. Accordingly, applicants argue that Wilson does not anticipate present claims 27 and 28.

Rejection under 35 USC § 102(b)

U.S. Patent No. 5,752,019 (Rigoutsos)

The Examiner has rejected former claims 1, 7, 16, 17 and 27 for lacking novelty over Rigoutsos, U.S. Patent No. 5,752,019.

Applicants respectfully disagree that Rigoutsos anticipates the presently claimed invention. Rigoutsos describes (a) a method for storing reference molecules in a computer

database and b) a method for determining the identity of reference molecules that are structurally or sub-structurally similar to the test molecule.

In Rigoutsos, the reference molecule and test molecule are broken down into a list of rigid substructure pairs separated by a rotatable bond. Each pair is further broken down into two 'substructure-tuple-selection-sets': Each substructure-tuple-selection-set is broken down to tuples which are atomic subsets of the 'substructure-tuple-selection-set'. Attributes of the 'tuples', including geometric information, are used to create a unique index for a unique tuple. Each tuple would have a vector that allows the transformation of the local coordinate back to the global coordinate.

In contrast to Rigoutsos' tuple index, the present invention stores each reference molecule under Cartesian or distance geometry coordinates. Further, the matching process in Rigoutsas is performed by matching the indices of the test-molecule tuples against the reference-molecule tuples, while the matching of the present invention is performed by comparing the distances between Cα-Cβ vectors. Accordingly, the present invention can handle a query comprising disconnected Cα-Cβ vectors whereas the Rigoutsos method would have difficulty breaking this up to list of pair of 'rigid substructures' separated by a rotatable bond, 'substructure -tuple-selection-set', and tuples.

Applicants further note that Rigoutsos teaches database searching methodology focussed on non-protein, small molecules. More particularly, Rigoutsos, unlike the present invention, does not disclose the creation of databases containing cysteine-rich framework proteins where amino acid side chains are simplified as Cα-Cβ vectors.

Regarding claims 31-38, we note that Rigoutsos describes database searching to identify "hits" that mimic proposed biologically-relevant conformation of a small molecule. These hits are not identified on the basis of structural similarity to the 3D structure of a protein. Furthermore, there is no subsequent engineering of the hit. Instead, ligands that fit a binding site are sought by Rigoutsos. In contrast, the presently claimed invention sculpts amino acid residues from a sample protein query onto the framework protein identified by database searching. Accordingly, Rigoutsos does not anticipate the present invention.

U.S. 4,853,871 (Pantoliano)

The Examiner has rejected former claims 1-13, 16, 18, 27 and 28 as being not novel over Pantoliano.

Referring to column 3 of Pantoliano, the goal of this patent is "to provide a method for determining whether the active folded state of a protein would be stabilized by the presence of a disulfide bond between particular regions of the protein molecule". The method of Pantoliano comprises five general steps.

The "First general step" is the creation of a library of naturally occurring disulfide geometries from the PDB. In particular, for each unique disulfide bond in the PDB, the coordinate for the relevant atoms (N_i, $C_{\alpha i}$, $C_{\beta i}$, C_i', S_i, O_i, N_{i+1} where i is the residue number) of each of the two cysteine residues are stored. From these coordinates, one can calculate the dihedral angle, Chi_3, along the bond which joins the two sulphur atoms (see column 7). One can also calculate the distance, $d_{CENTROID}$, between the two centroids of the two pyramids formed by the four atoms (N, C_α, C_β, C') of the two disulfide bridged cysteine residues (column 8).

In the "Second general step", the library is used to determine candidate residue pairs from the test protein, with the goal of replacing at least one of the residues in the pair with a cysteine to form a protein-stabilizing disulfide bridge (column 8). This is achieved by comparing the $d_{CENTROID}$ of the test-pair with that in the library. If a similar $d_{CENTROID}$ is found, then a structural comparison of the test-pair and the matched-pair is performed using Root-Mean-Square-Deviation fit of the eight atoms of the two pyramids in the test-pair with the eight atoms in the matched-pair (column 8).

In the "third to fifth general step", the validity and score of the matched pairs are determined by examining the steric hindrances (3^{rd}), the ranking by an expert in the field (4^{th}), and the evolutionary conservation of the residues in the matched test-pairs (5^{th}; columns 8 and 9).

Unlike the Pantoliano database, which is restricted to presenting the co-ordinates of the disulfide bridged cysteine residues of each entry, the present invention recognizes multiple relevant coordinates within each entry molecule. The search in Pantoliano is done by comparison

of the $d_{CENTROID}$ of the two pyramids, followed by Root-Mean-Square-Deviation of the eight atoms of the two pyramids. In contrast, the presently claimed invention is based on the comparison of the distances between Cα-Cβ vectors by a modified clique-detection algorithm. Accordingly, the presently claimed Cα-Cβ vector simplification of amino acid side chain location and orientation in 3D space is a much more flexible and generally useful system compared to the dual pyramid representation of Pantoliano.

Crucially, the results from searching as taught by Pantoliano is a list of ranked residue pairs in the test protein that are predicted to form a stabilizing disulfide bridge. In contrast, present claim 1 identifies one or more framework protein "hits" that potentially can act as new scaffolds forming the basis for subsequent engineering to mimic the sample protein. Unlike Pantoliano, which searches for residues capable of forming a stabilized disulfide bond, claim 1 step (ii) recites the creation of a query searching for the amino acid residues required for a specific function of a sample protein. Thus, the aim of Pantoliano is completely different to that of the present invention, as are the methods whereby Pantoliano seeks to achieve this aim.

Accordingly, applicants argue that the present claims are novel.

Lauri et al. J. Comp. Aid. Mol. Des. (1994)

The examiner has rejected former claims 1, 2, 7, 16 and 27 as anticipated by Lauri et al.

Applicants argue that the listing of the molecules in the database as relevant vector pairs (b_1-t_1, b_2-t_2) indexed according to protein structure in Lauri, is unlike the presently claimed invention's 3D coordinates for the Cα-Cβ vectors. Accordingly, Lauri does not anticipate the present invention.

The search in Lauri is done by breaking down the query into a list of binned and indexed vector pair (b_1-t_1, b_2-t_2), followed by finding hits that contain a large number of matching vector pairs. The match is done by a comparison of the index of the query vector pair with the index of the vector pair of the molecules in the database. In contrast, the presently claimed invention is based on a comparison of the unbinned distances between Cα-Cβ vectors by a clique-detection algorithm. This is particularly relevant to claim 27.

Secondly, with regard to claim 1 and its related dependent claims, Lauri does not teach the creation of a searchable database which includes a plurality of entries corresponding to a description of a location and orientation in 3D space of side chains of amino acid residues of a framework protein comprising 70 amino acids or less with 1-11 disulfide bonds.

Thirdly, with regard to claim 31 and its related dependant claims, Lauri does not teach modification of a framework protein "hit" identified by searching of the database recited in claim 31(i) or the subsequent determination of stability or function compared to the sample protein query (claims 34, 36) or increasing the degree of structural similarity to the sample protein (claim 35).

Applicants, therefore, respectfully submit that all claims are novel in light of Lauri.

US 5,643,564 (Hamaguchi)

The examiner has cited Hamaguchi against former claims 18 and 19, which have now been deleted. This rejection is therefore moot.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

If any fees are due in connection with the filing of this Amendment, please charge the fees to our Deposit account No 19-0741. If a fee is required for an extension of time under CFR § 1.136 that is not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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